FINDING OF NO SIGNIFICANT IMPACT

for

Ralgro Magnum (72 mg Zeranol)
for Feedlot Cattle

NADA 38-233

Schering-Plough
Animal Health
Union, NJ

For Public Display
(HFA-305)

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The Center for Veterinary Medicine has considered the potential environmental impact of this action and has concluded that this action will not have a significant impact on the quality of the human environment and therefore an environmental impact statement will not be prepared.

Schering-Plough Animal Health has submitted a supplemental new animal drug application (NADA) for the approval of 72 mg zeranol in feedlot cattle for improved feed conversion. The product is currently approved at the proposed dose for increased rate of weight gain (21 CFR 522.2680). In support of the application, the drug sponsor has submitted an environmental assessment (EA), dated December 9, 1998.

The EA provides information on the increase use of the product that may result from the new indication. Information in the EA indicates that the increase in use will not be substantial and that environmental impacts are not expected. The EA is also adequate to determine that future supplements for zeranol should be categorically excluded under 21 CFR 25.33(a) unless a substantial increase in the dosage is requested or extraordinary circumstances are identified.

We have reviewed the EA and find that it is adequate to determine that significant environmental impacts are not expected from the approval of the supplemental NADA for the product.

1/22/99
Date

Director, Office of New Animal Drug Evaluation, HFV-100

Attachment: EA dated December 9, 1998

ENVIRONMENTAL ASSESSMENT

FOR

ADDITIONAL INDICATION FOR "IMPROVED FEED EFFICIENCY" FOR RALGRO® MAGNUM™ EAR IMPLANTS FOR CATTLE

SECTION 1.	**DATE:**	December 9, 1998
SECTION 2.	**NAME OF APPLICANT/PETITIONER:**	Schering-Plough Animal Health Corp.
SECTION 3.	**ADDRESS:**	1095 Morris Ave. Union, NJ 07083-1982

SECTION 4. DESCRIPTION OF THE PROPOSED ACTION:

The applicant proposes to add to its approved label INDICATIONS statement, "for improved feed efficiency" for its 72 mg zeranol implant marketed under the trade name of RALGRO® MAGNUM™ (NADA 038-233).

This claim, if approved, could lead to increased use of the product by causing an increase in the number of sites where the product is used, but it would not increase the use of this product at an individual site.

The RALGRO® MAGNUM™ product was approved April 6, 1995 with the INDICATIONS statement, "for increased rate of gain." For that approval, the submitted and accepted Environmental Assessment (EA) estimated a 25% increase in environmental exposure of zeranol from the use of this product over that due to use of all other zeranol cattle implants in the U.S. (the only approved product being the 36 mg RALGRO® implant). Based on 1997 sales records, the actual increase was less than 2%.

The percent increase in yearly use of RALGRO® MAGNUM™ implants due to approval of the additional "improved feed efficiency" claim is estimated to be at most 3%. Therefore, the previously approved "increased rate of gain" claim and this additional "improved feed efficacy" claim together would increase the overall environmental exposure by only 5% rather than the 25% which was predicted in the EA which was submitted in support of the April 6, 1995 approval and found acceptable.

Based upon the proposed action, zeranol could potentially be introduced into the following environments:

a. The environment adjacent to the Terre Haute, IN, manufacturing facility. (Since the manufacturing facility is under the jurisdiction of other regulatory agencies, it will not be further addressed here.)
b. Agricultural lands where waste products from cattle feedlots are used as fertilizers.
c. Aquatic systems where run-off is collected from sites receiving waste products from cattle feed lots.

SECTION 5. IDENTIFICATION OF CHEMICAL SUBSTANCES THAT ARE THE SUBJECT OF THE PROPOSED ACTION:

Chemical Name: (3S, 7R) -3, 4, 5, 6, 7, 8, 9, 10, 11, 12-decahydro-7, 14, 16-trihydroxy-3-methyl-1H-2-benzoxacyclotetradecin-1-one

CAS Registry Number: 26538-44-3

Molecular Formula: $C_{18}H_{26}O_5$

Molecular Weight: 322. 40

Meting Point: 181-185°C

pKa Values: 8.44 and 11.42 with 1% methanol as co-solvent

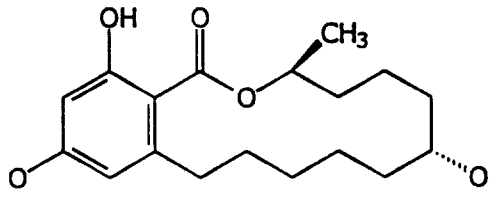
Aqueous Solubility: 4.13 µg/mL at pH 5.0
5.14 µg/mL at pH 7.0
27.8 µg/mL at pH 9.0

Vapor Pressure: 3.9×10^{-9} torr

N-octanol/Water Partition Coefficient: Log P_{ow} 3.13 at pH 5.0 & 7.0
P_{ow} 3.47 at pH 9.0

Ultraviolet Spectrum: UV maxima at 218, 265, 304 nm

Structural Formula:



SECTION 6. INTRODUCTION OF THE SUBSTANCES INTO THE ENVIRONMENT:

The routes by which zeranol will be introduced into various compartments of the environment and the concentration in those compartments has been discussed in detail in previous environmental assessments (see EA for original Ralgro Magnum product approved on April 6, 1995).

Zeranol from use in cattle will be introduced into the environment primarily through the use of manure from zeranol treated cattle as fertilizer. This claim of improved feed efficiency from RALGRO® Magnum™ will not increase the number of animals treated at a site currently using the RALGRO® Magnum™, although it may encourage other producers to use it on their cattle. Hence, the concentration of zeranol on the individual feedlot basis is the same as that previously discussed.

The concentration of zeranol residues in soil would be 0.09 μg/kg soil.

SECTION 7. FATE OF THE EMITTED SUBSTANCES IN THE ENVIRONMENT:

Fate data on zeranol was discussed in detail in previously accepted environmental assessments (see EA for original Ralgro Magnum product approved on April 6, 1995). The key finding was that zeranol degrades rapidly in both manure and soil.

Zeranol is mineralized to CO_2 with half lives of 49-91 days (3 soils). It degrades in soil with half lives of approximately <7 to 30 days.

From the above studies it can be concluded that any zeranol present will rapidly degrade in both manure and soil. After 56 days approximately 50% of the zeranol initially present in manure is degraded. This degradation continues after field application of manure. Ninety days after field application 50% of the applied zeranol has mineralized to CO_2. The zeranol that has not been degraded all the way to CO_2 would be expected to bind to the soil and not migrate into water systems. Therefore zeranol will not be present in the environment for a substantial period of time.

SECTION 8. ENVIRONMENTAL EFFECTS OF RELEASED SUBSTANCES

The environmental effects of zeranol were described in detail in previous EAs (see EA for original Ralgro Magnum product approved on April 6, 1995). The NOELs observed were in the high ppm level compared to the very low concentrations (less than 0.1 ppb) in the environment.

The approval of this requested action would not result in increased use of the product at sites already using it, but would result in only a minor overall increase. From the data on environmental fate and effects, it is concluded that zeranol will not have an adverse effect on the environment due to rapid degradation. Zeranol may be present in the environment at extremely low levels. The zeranol that is introduced into the environment will be rapidly mineralized to CO_2 by normal terrestrial organisms. Zeranol will have no effect on terrestrial organisms while it is undergoing rapid mineralization. The additional zeranol entering into the environment due to this use would follow the same fate with no additional impact on the environment.

SECTION 9. USE OF RESOURCES AND ENERGY:

Manufacturing zeranol will require an amount of energy similar to that used to produce and package any conventional pharmaceutical product for animals. Disposal of waste washwater and materials from the manufacturing process will not require use of unusual amounts of energy or natural resources. There will be no effects upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

SECTION 10. MITIGATION MEASURES:

As there are no known or expected adverse effects of the proposed action, no mitigation measures will be required.

SECTION 11. ALTERNATIVES TO THE PROPOSED ACTION:

The proposed action would not be expected to have any substantial adverse effect on human health or the environment. Therefore, alternatives to the proposed action do not need to be considered.

SECTION 12. LIST OF PREPARERS:

The following personnel from Schering-Plough Animal Health Corp. was responsible for the preparation of this Environmental Assessment:

Peter Wislocki, PhD
Senior Director
Drug Safety and Metabolism
Schering-Plough Research Institute

SECTION 13. CERTIFICATION:

The undersigned official certifies that the information presented in the Environmental Assessment is true, accurate and complete to the best of his knowledge.

12-9-98

A.P. Shaffer, DVM
Manager, Regulatory Affairs
Schering-Plough Animal Health Corp.

NADA 038-233
Amendment to an Unapproved Supplement to an Approved Application
Environmental Assessment

ENVIRONMENTAL ASSESSMENT: Regulatory Chronology

The following is a summary of previous communication under NADA 038-233 pertaining to environmental assessment (EA) for the addition of the label claim of "improved feed efficiency."

DATE	Description of Correspondence
6/4/97	SPAH submits supplement for new label claim.
12/5/97	(phone conference with C. Eirkson) CVM provides guidance on drafting of EA.
2/27/98	SPAH submits revised environmental assessment in an "Amendment to an Unapproved Supplement to an Approved Application" at the request of CVM.
4/14/98	(phone conference with C. Eirkson) CVM provides further guidance on the submitted EA, and recommends resubmission of revised version.
11/11/98	(via fax) SPAH submits desk copy of revised draft EA to C. Eirkson.
11/25/98 and 12/3/98	(phone conferences with C. Eirkson) CVM provides further guidance on EA, and recommends submission of final revised version.
12/11/98	SPAH submits revised EA to NADA 038-233 as an "Amendment to an Unapproved Supplement to an Approved Application."